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METHOD FOR PREDICTION OF PATIENT RESPONSE TO MEDICATION IN PSYCHIATRIC DISORDERS

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Cross reference to related applications

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ABSTRACT

The inventors have developed and implemented a unique method for computerized analysis of an individual patient's electroencephalogram (EEG) recorded by electrodes placed on the scalp, for the purpose of predicting patient response to administration of medications and therapeutic agents commonly used in psychiatric practice. The business entity offering this technology commercially is NuPharm Database, LLC.

The prediction of the nature of responses to medications (adverse, no effect, favorable outcome) is an important problem in the clinical practice of psychiatry. A growing number of therapeutic agents are available to the clinician but these agents generate variable responses when prescribed based solely on the patient's history and current symptoms. The inventor's technology is used by physicians to improve patient outcome by selecting agents most likely to be effective for a given patient, using a standardized analysis of the digitized EEG and comparison of individual patient EEG data to a particular database of similar patients whose clinical outcome to pharmacotherapy is known. The patient is required to be medication free at the time of the recording.

METHOD FOR PREDICTION OF PATIENT RESPONSE TO MEDICATION IN PSYCHIATRIC DISORDERS

FIELD OF THE INVENTION

The methodology developed by the inventors, involves recording the EEG in a digital format from a patient diagnosed with a psychiatric disorder, the packaging and transmittal of the computer file containing the EEG and patient information to a report processing center via the Internet, generation of a proprietary, probabilistically based medication responsivity report, and the return transmission of the report to the recording site via the Internet. EEG signals contained in computer files are not transmitted in real time but rather following the recording, "off-line". More specifically, the following steps are employed:

1) The EEG is recorded using electrodes placed on the patient's scalp, and the EEG data is stored in a digital format using a standardized protocol available on one of a number of commercially available instruments (current manufacturers include Cadwell Laboratories, Bio-Logic Systems Corp., Nicolet Biomedical, Oxford Instruments, among others). The International 10-20 System convention is used for determining the location of electrodes placed on the scalp. It is the responsibility of the recording facility to collect data in accordance with the NuPharm DataBase procedural specifications.

2) The following patient criteria apply:

a) Patient must have received a psychiatric diagnosis as specified in the Diagnostic and Statistical Manual, currently the Fourth Edition (DSM-IV).

b) Ages between six and ninety.

c) Patient is taking no medications. All medications potentially influence the EEG and must be discontinued or avoided for seven half-lives prior to baseline EEG examination. This includes "over the counter" sleeping pills, pain medication, nutritional health supplements and mega-vitamins. A reference list of the most commonly used medications and associated half-lives is available from the NuPharm Database Report Processing Center.

c). Insulin, thyroid, estrogen, progesterone and other hormone replacement agents are not excluded. Some cardiac agents are included in the reference population of after the age of fifty-five. Further information about use of these agents is available from the NuPharm Database Report Processing Center.

d) Patients with any of the characteristics listed below are not suitable for prediction of medication responsivity based on EEG analysis:

(i) intramuscular depo-neuroleptic therapy within the preceding twelve months

(ii) a history of craniotomy with or without metal prostheses

(iii) a history of cerebrovascular accident

(iv) spikes or extreme low voltage on the conventional EEG

(v) a current diagnosis of seizure disorder

(vi) a diagnosis of dementia

(vii) mental retardation

(viii) current use of marijuana, cocaine, hallucinogens or other drugs of abuse

(ix) inability to remain medication-free and drug-free for seven half-lives of the current agent(s) prior to EEG recording

(x) significant abnormality of the CBC, chemistry or thyroid panel with TSH until corrected

e) A "positive" Urine Drug Screen (UDS) interferes with medication prediction methods. Studies are processed only if the UDS is negative just prior to recording the digital EEG.

3) The digital EEG data computer file is packaged along with additional patient identifying information using proprietary NuPharm Database LLC software currently called "Site Commander". The patient information includes:

a) name
b) date of birth
c) referring physician
d) handedness
e) height
f) weight
g) date of test
h) patient ID (social security number)

Packaging refers to compression of the computer file and encryption of the file so that it cannot be opened or examined by anyone other than at the NuPharm Database processing center. The data transfer is rigorously secured to protect the confidentiality of patient records. The EEG files are encrypted at the recording facility with a key known only to NuPharm Database LLC. The patient ID is transformed using a proprietary algorithm so

that even in the case of mail routing error there is no way to associate the data with an individual. The data is compressed and protected with an additional password and data files are transmitted to a secure site. These steps mean that the patient data are protected against even purposeful attempts to intercept and read them.

The transmittal of the EEG file and related patient information is tracked as it is packaged, sent, processed, and returned. All log entries include dates and times calibrated to GMT. This system is Y2K compliant.

The computer operating system required to run the proprietary NuPharm Database EEG and report transmission software is currently Microsoft Windows 95/98. The following hardware and software is required to run the Site Commander program:

Hardware Requirements

Operating System: Windows 95 or Windows 98
Processor: 486, 133 MHz.
Monitor and Video Card capable of displaying 256 colors.
Disk Space: 35 MB
RAM: 16 MB
CD-ROM Drive if installing from CD-ROM
Modem: 33.6 KBaud
Internet Connection with approved Internet Service Provider

Software Requirements

Adobe Acrobat Reader Version 3.01 (included on distribution CD-ROM)
Microsoft Internet Explorer 4.0 or above (included on distribution CD-ROM)
Site Commander Software from NuPharm DataBase LLC (included on distribution CD-ROM)

4) The computer file is transferred off-hours using standard commercially available file transfer protocols (FTP) via the Internet, to a designated site administered by NuPharm Database. A special feature of the Site Commander software exists to allow immediate transfer of files for priority reporting if requested by the client. NuPharm Database monitors the transfer site in order to detect the arrival of new computer files. When a new file is received, it is forwarded to the NuPharm Database Reporting Center for professional interpretation, if requested, and specialized report generation.

5) The file is decompressed and decrypted at the NuPharm Reporting Center . Experienced technical and professional personnel then review the EEG signals and sections of the recording identified as containing signals generated by extracerebral sources are deleted from subsequent analyses. The samples of EEG selected for inclusion in analysis are then passed to the first stage of analysis.

6) The first stage of analysis includes computations that extract a standard set of features from the EEG. Quantitative spectral analysis provides commonly used measures of EEG power

and relative power. Power is the square of amplitude; amplitude units are in microvolts (μV), power units are microvolts squared(μV^2). Relative power is a measure of the proportion of power in a given frequency band compared to the total band power at a given electrode. Frequency bands are defined as delta, .5 - 2.5 Hz.; theta, 2.5 - 7.5 Hz.; alpha, 7.5 - 12.5 Hz., and beta, 12.5 - 32 Hz. The total band is .5 to 32 Hz.

EEG coherence, a commonly used measure of the similarity of activity for a pair of two scalp electrodes, also is extracted by spectral analysis for all interhemispheric and intrahemispheric sets of electrode pairs, for each frequency band as defined above.

Commonly used measures of peak frequency within each defined frequency band are computed.

Combinations of power and coherence measures over defined sets of scalp electrodes are also computed.

7) Features extracted from individual EEG data by quantitative spectral and statistical analysis are further compared to two distinct databases. In the second stage of analysis, Z-scores representing deviations from a nonsymptomatic reference population are computed. This reference population, often referred to as the "Neurometric" database, contains 2082 quantitative EEG measures including absolute power, relative power, coherence, symmetry, and mean frequency of the delta, theta, alpha and beta frequency bands of the EEG at every electrode position of the International 10-20 System for individuals from 6 to 92 years (database #1). The z-score value obtained by comparison of individual's data to the age appropriate subset of the database represents the patient's statistical deviation from the reference database.

8) The third stage of processing involves medication response prediction using the patient database compiled by NuPharm Database LLC (database #2). This prediction is made by first identifying the pattern of EEG deviations from the reference database. Individual patient deviation is then compared with the characteristic features of the population of patients whose medications and treatment outcomes are known. A proprietary rule-based classifier is applied to estimate the likelihood that a patient EEG contains a pattern known to be responsive to a given agent, class of agents, or combination of agents or classes of agents. The EEG variables currently used by the classifier are shown in Tables 1-4, below.

Column Heading	Description of Abbreviation	Column Heading	Description of Abbreviation
Table 1		**Table 2**	
RMAD	Relative power monopolar anterior delta	FMAD	Frequency monopolar anterior delta
RMPD	posterior delta	FMPD	posterior delta
RMAT	anterior theta	FMAT	anterior theta
RMPT	posterior theta	FMPT	posterior theta
RMAA	Anterior alpha	FMAA	anterior alpha
RMPA	Posterior alpha	FMPA	posterior alpha
RMAB	Anterior beta	FMAB	anterior beta
RMPB	posterior beta	FMPB	posterior beta
CEAD	Coherence interhemispheric anterior delta	AADL	Asymmetry intrahemispheric delta - left
CEPD	Posterior delta	AADR	delta - right
CEAT	anterior theta	AATL	theta - left
CEPT	posterior theta	AATR	theta - right
CEAA	anterior alpha	AAAL	alpha - left
CEPA	Posterior alpha	AAAR	alpha - right
CEAB	Anterior beta	AABL	beta - left
CEPB	posterior beta	AABR	beta - right

Table 3		**Table 4**	
AED	Asymmetry monopolar interhemispheric delta	CEBD	Coherence interhemispheric bipolar delta
AET	Theta	CEBT	Theta
AEA	Alpha	CEBA	Alpha
AEB	Beta	CEBB	Beta
AEBD	Asymmetry bipolar interhemispheric delta	RBDL	Relative power bipolar delta left
AEBT	Theta	RBDR	Delta – right
AEBA	Alpha	RBTL	Theta -left
AEBB	Beta	RBTR	Theta – right
CADL	Coherence intrahemispheric delta -left	RBAL	Alpha - left
CADR	Delta - right	RBAR	Alpha - right
CATL	Theta - left	RBBL	Beta- left
CATR	Theta -right	RBBR	Beta - right
CAAL	Alpha - left		
CAAR	Alpha - right		
CABL	Beta - left		
CABR	Beta - right		

9) A formal report for the referring clinician is generated. The report is returned in a format that cannot be modified by the client (Adobe Systems, Inc., "portable document format", or "PDF"). This report contains certain elements as specifically requested by the referring clinician. These elements may include a professional medical interpretation of the digital EEG tracing, a presentation of selected features extracted by quantitative EEG analysis, a presentation of deviations from the Neurometric database, and a statement of the likelihood of favorable pharmacotherapeutic outcome based on comparison with patients having similar EEG features in the NuPharm Database. The treating physician is responsible for any medication selection, titrating of dosage and monitoring the patient for side effects and is instructed to incorporate results of reports with the psychiatric assessment to develop into an overall clinical treatment plan.

10) The report is returned to the transfer site administered by NuPharm Database and may be downloaded by the client on a regular schedule, using proprietary NuPharm Database software, Site Commander, for viewing and printing the report by the client at the recording site. PDF files are opened and displayed using an interface to Adobe Acrobat Reader (TM) software. Reports may be printed on any operating system compatible printer.

11) Follow up EEG recordings can then be used to track changes produced by administration of medications by repeating the entire process outlined above. For follow up studies, the patient also is interviewed by the treating physician and Clinical Global Improvement (CGI) is scored. A score of -1 indicates an adverse effect, 0 no improvement, 1 minimal or mild improvement, 2 moderate improvement, and 3 marked improvement or remission of symptoms. The CGI scores are sent to the NuPharm Database analysis center and are reported along with changes, expressed as difference scores, on variables shown in Tables 1-4 above.

We claim:

1. A unique system for compressing, encrypting, tracking, and securely transmitting digital EEG data and associated patient identifying information via the Internet from a remote site to a Report Processing Center, and including the electronic return of a report summarizing results of proprietary analyses and database comparison all without requiring telephonic transmission.

2. Identification of a set of univariate and multivariate EEG features that when observed in a patient diagnosed with a psychiatric disorder, can be used with NuPharm Database's particular rule-based classifier to predict a favorable clinical responsive to psychostimulant class medications.

3. Identification of a set of univariate and multivariate EEG features that when observed in a patient diagnosed with a psychiatric disorder, can be used with NuPharm

Database's particular rule-based classifier to predict a favorable clinical responsive to antidepressant class medications.

4. Identification of a set of univariate and multivariate EEG features that when observed in a patient diagnosed with a psychiatric disorder, can be used with NuPharm Database's particular rule-based classifier to predict a favorable clinical response to anticonvulsant class medications.

5. Identification of a set of univariate and multivariate EEG features that when observed in a patient diagnosed with a psychiatric disorder, can be used with NuPharm Database's particular rule-based classifier to predict a favorable clinical responsive to a combination of psychostimulant and antidepressant class medications.

6. Identification of a set of univariate and multivariate EEG features that when observed in a patient diagnosed with a psychiatric disorder, can be used with NuPharm Database's particular rule-based classifier to predict a favorable clinical responsive to a combination of anticonvulsant and antidepressant class medications.

7. Identification of a set of univariate and multivariate EEG features that when observed in a patient diagnosed with a psychiatric disorder, can be used with NuPharm Database's particular rule-based classifier to predict a favorable clinical response to a combination of psychostimulant, antidepressant, and anticonvulsant class medications.

4 8. A method for computerized generation of clinical reports that integrates interpretive information from medical professionals with results of medication responsivity evaluation according to claims 2 thru 7

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